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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Alexandre HUBOUX

Confirmation No.: 8745

Patent No.: 7,019,152 B2

Application No.: 10/820,709

Patent Date: March 28, 2006

Filing Date: April 9, 2004

For: PROCESS FOR THE OPTICAL
RESOLUTION OF A PRECURSOR
OF SCLAREOLIDE

Attorney Docket No.: 81455-5730

**REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 C.F.R. §§ 1.322 and 1.323**

Certificate

APR 10 2006

of Correction

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Patentee hereby respectfully requests the issuance of a Certificate of Correction in connection with the above-identified patent. The corrections are listed on the attached Form PTO-1050. The corrections requested are as follows:

Title Page:

Item [56] **References Cited**, OTHER PUBLICATIONS,

“T Sukasa Koga et al.” reference, change “T Sukasa” to -- Tsukasa --; and change “AmbrokR” to -- Ambrox® --.

These changes are to correct inadvertent errors of a clerical or typographical nature.

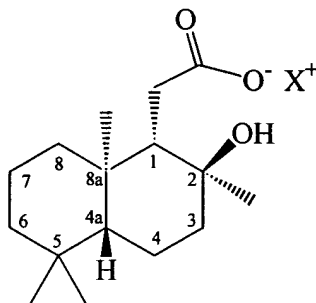
04/06/2006 JADD01 00000002 501814 7019152
01 FC:1811 100.00 DA

APR 11 2006

Column 1:

Lines 29-39, delete formula (I') and insert the following:

(I')

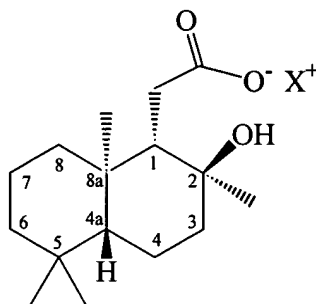


Support for this change appears on page 1 of the specification.

Column 2:

Lines 36-46, delete formula (I') and insert the following:

(I')

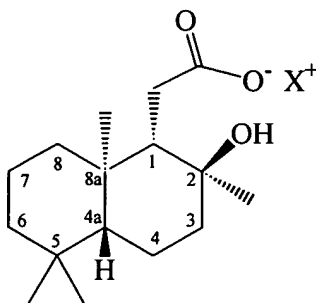


Support for this change appears on page 1 of the specification.

Column 7:

Lines 26-36, delete formula (I') and insert the following:

(I')



Support for this change appears in original application claim 1.

Line 52 (claim 2, line 13), delete " pK_a " and insert -- pK_a --. Support for this change appears in original application claim 2.

A fee of \$100 is believed to be due for this request. Please charge the required fees to Winston & Strawn LLP Deposit Account No. 50-1814. Please issue a Certificate of Correction in due course.

Respectfully submitted,

4/5/06
Date

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Customer No. 28765

212-294-3311

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.: 7,019,152 B2
DATED: March 28, 2006
INVENTORS: Huboux

Page 1 of 2

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page,

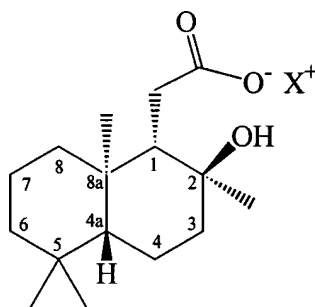
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"T Sukasa Koga et al." reference, change "T Sukasa" to -- Tsukasa --; and change "AmbrokR" to -- Ambrox® --.

Column 1,

Lines 29-39, delete formula (I') and insert the following:

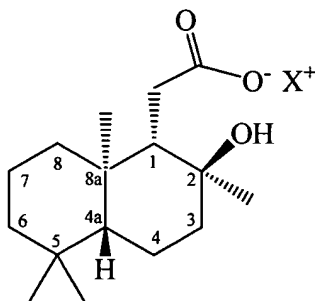
(I')



Column 7,

Lines 36-46, delete formula (I') and insert the following:

(I')



UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.: 7,019,152 B2
DATED: March 28, 2006
INVENTORS: Huboux

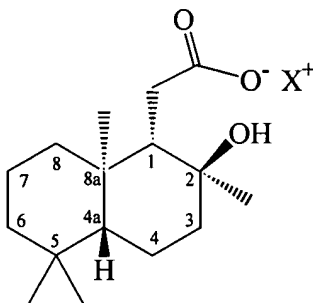
Page 2 of 2

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 7,

Lines 26-36, delete formula (I') and insert the following:

(I')



Line 52 (claim 2, line 13), delete "pK_a" and insert -- pK_a --.



US007019152B2

(12) **United States Patent**
Huboux

(10) **Patent No.:** **US 7,019,152 B2**
(45) **Date of Patent:** **Mar. 28, 2006**

(54) **PROCESS FOR THE OPTICAL RESOLUTION
OF A PRECURSOR OF SCLAREOLIDE**

(75) **Inventor:** **Alexandre Huboux**, Pringy (FR)

(73) **Assignee:** **Firmenich SA**, Geneva (CH)

(*) **Notice:** Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 146 days.

(21) **Appl. No.:** **10/820,709**

(22) **Filed:** **Apr. 9, 2004**

(65) **Prior Publication Data**

US 2004/0192960 A1 Sep. 30, 2004

Related U.S. Application Data

(63) Continuation of application No. PCT/IB03/02933,
filed on Jul. 24, 2003.

(30) **Foreign Application Priority Data**

Jul. 31, 2002 (WO) PCT/IB02/03055

(51) **Int. Cl.**

C07C 61/13 (2006.01)

C07D 307/92 (2006.01)

(52) **U.S. Cl.** 549/299; 549/204; 562/402;
562/466

(58) **Field of Classification Search** 562/462,
562/497, 501, 402, 466; 549/204, 299
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,247,100 A * 9/1993 Gerke et al. 549/299
5,290,955 A * 3/1994 Asanuma et al. 549/458
5,347,048 A * 9/1994 Asanuma et al. 562/501
5,525,728 A * 6/1996 Schneider et al. 549/299

FOREIGN PATENT DOCUMENTS

EP 0 550 889 A1 7/1993
WO WO 93/21174 10/1993

OTHER PUBLICATIONS

Article, XP-002256238, Ephedrin, PD 00-00, pp. 1181-1182
(1997).

T Sukasa Koga et al. XP004143697 "Resolution of
sclareolide as a key intermediate for the synthesis of
AmbrokR Tetrahedron, Asymmetry, Elsevier Science
Publishers, Amsterdam, NL, vol. 9, No. 21, pp. 3819-3823
(1998).

Tsukasa

Ambrox®

* cited by examiner

Primary Examiner—Porfirio Nazario-Gonzalez

(74) *Attorney, Agent, or Firm*—Winston & Strawn LLP

(57) **ABSTRACT**

The present invention relates to the field of organic synthesis
and more particularly to a new process for the optical
resolution of a precursor of sclareolide. This process
includes the reaction of [(1RS,2RS,4aSR,8aSR)-2-hydroxy-
2,5,5,8a-tetramethyldecahydronaphthalen-1-yl]acetic acid,
or an alkaline salt thereof, with an enantiomer of the
2-(methlamino)-1-phenyl-1-propanol, or an ammonium
salt thereof respectively, which is used as resolving agent.

9 Claims, No Drawings

ALL

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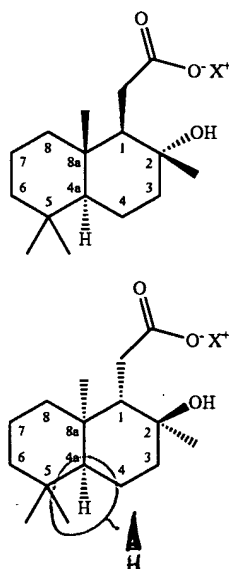
PROCESS FOR THE OPTICAL RESOLUTION OF A PRECURSOR OF SCLAREOLIDE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of International Application PCT/IB2003/002933 filed Jul. 24, 2003, the entire content of which is expressly incorporated herein by reference thereto.

TECHNICAL FIELD

The present invention relates to the field of organic synthesis and more particularly to a process for obtaining a compound of formula (I) or (I')



wherein X represents an optically active enantiomer of (2-hydroxy-1-methyl-2-phenylethyl)methylammonium;

using a racemic [(1R,2R,4aSR,8aSR)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl]acetic acid derivative as starting material. In other words, the invention's process concerns an optical resolution of a racemic [(1R,2R,4aSR,8aSR)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl]acetic acid derivative using, as resolving agent, an optically active enantiomer of 2-(methylamino)-1-phenyl-1-propanol.

BACKGROUND

[(1R,2R,4aS,8aS)-2-Hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl]acetic acid, from now on referred to also as (2R)-hydroxy-acid, may be a useful precursor of (+)-sclareolide, an intermediate in the synthesis of the perfumery ingredient (-)-Ambrox®.

Despite this fact, only few processes for the preparation of (2R)-hydroxy-acid, or a salt thereof, by optical resolution of a racemic [(1R,2R,4aSR,8aSR)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl]acetic acid, from now on referred to also as (2RS)-hydroxy-acid, or a salt thereof, have been reported in the prior art.

In EP 550 889 is reported a process for the optical resolution of (2RS)-hydroxy-acid in which a 1-(aryl)ethy-

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lamine is used as resolving agent. For the same process, but using the sodium salt of (2RS)-hydroxy-acid as starting material, Koga et al. in *Tetrahedron Asymmetry*, (1998), 9, 3819, report the use as resolving agent of some 1,2- or 1,3-amino-alcohols in addition to the previously cited 1-(aryl)ethylamine.

However, all the prior art procedures suffer from the disadvantages of needing complex procedures implying slow and complicated crystallization procedures and/or a re-crystallization. Consequently, low yields of the final product are frequently, if not always, observed.

Therefore, there is a need for a process capable of providing an optically active enantiomer of a (2RS)-hydroxy-acid, or a salt thereof, and being of improved efficiency.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In order to overcome the disadvantages of the prior art processes mentioned hereinabove, the present invention relates to a highly efficient process for obtaining a compound of formula (I) or (I')

(I)

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(I')

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wherein X represents an optically active enantiomer of (2-hydroxy-1-methyl-2-phenylethyl)methylammonium; said process being characterized in that

- it comprises the treatment of [(1R,2R,4aSR,8aSR)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl]acetic acid with an optically active enantiomer of 2-(methylamino)-1-phenyl-1-propanol, or the treatment of an alkaline salt of [(1R,2R,4aSR,8aSR)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl]acetic acid with an ammonium salt obtainable by the reaction of an optically active enantiomer of 2-(methylamino)-1-phenyl-1-propanol with an acid having a pK_a below 5; and
- said treatment is performed in a solvent wherein the compounds of formula (I) or (I') have different solubilities.

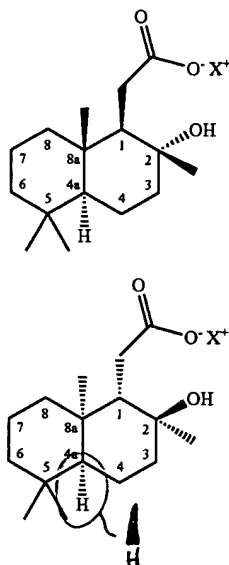
The expression " pK_a " has the usual meaning in the art, and in particular it represents $-\log_{10}K_a$, wherein K_a is the dissociation constant of an acid in water, at standard temperature and pressure.

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hydroxy-acid, were added 6.9 g of acetic acid and the reaction mixture was heated at reflux for 2.75 hours, using a Dean-Stark trap to remove water azeotropically. At the end of the reflux period, the reaction mixture was cooled to approximately 50° C., washed with 100 ml of water and then with 100 ml of 3% aqueous NaHCO₃. It was thus obtained an organic phase which, after evaporation of the solvent, provided 113.6 g (91% yield) of (+)-sclareolide having a purity >98% and an e.e.=99%, purity and e.e. being obtained by chiral GC. The NMR spectra of the product thus obtained were conform to those reported in the prior art.

What is claimed is:

1. A compound of formula (I) or (I')



wherein X represents an optically active enantiomer of (2-hydroxy-1-methyl-2-phenylethyl)methylammonium.

2. A process for obtaining a compound of formula (I) or (I'), as defined in claim 1, said process being characterized in that

a) it comprises the treatment of [(1RS,2RS,4aSR,8aSR)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl]acetic acid with an optically active enantiomer of 2-(methylamino)-1-phenyl-1-propanol, or the treatment of an alkaline salt of [(1RS,2RS,4aSR,8aSR)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl]acetic acid with an ammonium salt obtainable by the reaction of an optically active enantiomer of 2-(methylamino)-1-phenyl-1-propanol with an acid having a pK_a below 5; and

b) said treatment is performed in a solvent wherein the compounds of formula (I) or (I') have different solubilities.

3. A process according to claim 2, wherein the solvent is a C₆-C₉ aromatic solvent, a C₆-C₁₀ petroleum fraction or hydrocarbon, a C₁-C₂ halogenated solvent, a C₄-C₁₀ ether, a C₃-C₁₀ ester, a C₃-C₁₀ alcohol or mixtures thereof.

4. A process according to claim 3, wherein the solvent is selected from the group consisting of anhydrous tetrahydrofuran, toluene, xylene, benzene or cyclohexane.

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5. A process according to claim 2, wherein the optically active enantiomer of 2-(methylamino)-1-phenyl-1-propanol is (1R,2R)-2-(methylamino)-1-phenyl-1-propanol or (1S,2S)-2-(methylamino)-1-phenyl-1-propanol.

6. A process according to claim 2, wherein the acid having a pK_a below 5 is selected from the group consisting of HX, wherein X is a halide, H₂SO₄, HNO₃, H₃PO₄, HPF₆, HBF₄, HClO₄, C₁-C₁₀ sulphonic acids, and C₁-C₁₀ mono-, di- or tri-carboxylic acid.

7. A process for obtaining (+)-sclareolide or (-)-sclareolide which comprises treating a compound of formula (I) or (I'), respectively, as defined as in claim 1, with an acid having a pK_a below 5 and by a thermal treatment at a temperature comprised between 60° C. and 150° C.

8. A process for obtaining (+)-sclareolide or (-)-sclareolide said process being characterized in that it comprises

I) the hydrolysis of (±)-sclareolide into a corresponding [(1RS,2RS,4aSR,8aSR)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl]acetic acid or a salt thereof,

II) treatment of [(1RS,2RS,4aSR,8aSR)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl]acetic acid with an optically active enantiomer of 2-(methylamino)-1-phenyl-1-propanol, or the treatment of an alkaline salt of [(1RS,2RS,4aSR,8aSR)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl]acetic acid with an ammonium salt obtainable by the reaction of an optically active enantiomer of 2-(methylamino)-1-phenyl-1-propanol with an acid having a pK_a below 5; wherein either treatment is performed in a solvent to obtain a compound of formula (I) or (I'), respectively, according to claim 1; and

III) treating the compound of formula (I) or (I'), respectively, with an acid having a pK_a below 5 and by a thermal treatment at a temperature comprised between 60° C. and 150° C.

9. A process for obtaining a compound of formula (I) or (I'), as defined in claim 1, said process being characterized in that

a) it comprises the treatment of [(1RS,2RS,4aSR,8aSR)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl]acetic acid with an optically active enantiomer of 2-(methylamino)-1-phenyl-1-propanol, or the treatment of an alkaline salt of [(1RS,2RS,4aSR,8aSR)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl]acetic acid with an ammonium salt obtainable by the reaction of an optically active enantiomer of 2-(methylamino)-1-phenyl-1-propanol with an acid selected from the group consisting of HX, wherein X is a halide, H₂SO₄, HNO₃, H₃PO₄, HPF₆, HBF₄, HClO₄, C₁-C₁₀ sulphonic acids, and C₁-C₁₀ mono-, di- or tri-carboxylic acid; and

b) said treatment is performed in a solvent selected from the group consisting of a C₆-C₉ aromatic solvent, a C₆-C₁₀ petroleum fraction or hydrocarbon, a C₁-C₂ halogenated solvent, a C₄-C₁₀ ether, a C₃-C₁₀ ester, a C₃-C₁₀ alcohol or mixtures thereof.

* * * * *

APR 11 2006